January 13, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration, HHS
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re.: Request for Comments – **Docket No. 2004N-0432**

Dear Madam/Sir:

I am writing in response to the U.S. Food and Drug Administration's (FDA's) request for comments regarding the potential need to revise the FDA regulations (21 CFR 361.1) governing radioactive drugs for certain research uses.[1] Note also that I was in attendance at the FDA's Public Meeting (November 16, 2004) regarding these regulations, and that certain of my comments may be directed at statements or issues presented at this meeting.

I am a board-certified (Board of Pharmaceutical Specialties) nuclear pharmacist and an active member of the Society of Nuclear Medicine (SNM) and the Section on Nuclear Pharmacy of the American Pharmaceutical Association (APhA). My current employer is the University of Pittsburgh, where I serve as Director of the Research Conduct and Compliance Office and hold the academic positions of Professor and Assistant Dean, School of Pharmacy. I also serve as Chair of the University's Radioactive Drug Research Committee (RDRC). The comments below are, however, my personal comments and may not reflect the opinions of the SNM, APhA, or University of Pittsburgh.

I will attempt to comment on the various questions and issues addressed in the previously cited Federal Register notice; in the order presented:

1. *Pharmacology Issues*: It is noted that current Section 361.1(b)(2) requires that the amount of radioactive drug to be administered be known not to cause any clinically detectable pharmacological effect in humans. According to Section 361(d)(2), investigators must provide pharmacological dose calculations based on published literature or other human data to demonstrate an absence of a clinically detectable pharmacological effect.

   As discussed at the Public Hearing, adherence to these provisions of 21 CFR 361.1 precludes first in human evaluations of radioactive drugs, which presents a significant limitation to the number of physiological or pathophysiological processes that can be studied under this regulatory framework and/or the extension of this regulatory framework to permit initial pharmacokinetic evaluations of potential (radioactive) diagnostic imaging agents and (radioactive and non-radioactive) therapeutic agents. Thus, I am supportive of a revision to the 21 CFR 361.1 regulations to permit first in human studies of radioactive drugs administered at "microdose" levels; such levels

[1] Federal Register 69 (No. 102), 59569-59572, October 5, 2004.

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being based on an appropriate small fraction of the dose inducing a minimal toxic effect in valid, limited animal toxicity studies. Note that the term "valid" implies that these animal toxicity studies would be conducted in accordance with the FDA's current Good Laboratory Practice standards (cGLPs). The term "limited" should take into account the fact that the radioactive drugs being studied under this regulatory framework will typically be administered only a few times over the course of a year; thus minimizing the requirement for extensive, chronic preclinical toxicity evaluations.

Regarding the extent of the animal toxicity data required and the fraction of the minimal toxic dose that would constitute a "safe" microdose for first in human studies, it is recommended that the FDA consider the adoption of respective European Medicines Agency (EMEA) and International Conference on Harmonization (ICH) M3 recommendations.[2] This approach would be consistent with current efforts to harmonize internationally the regulations that govern the drug development and approval process. It would also minimize the current practice of "international regulation shopping", wherein certain U.S. investigators have chosen to conduct initial human evaluations of radiotracers in foreign countries that have less restrictive regulatory requirements than those of the FDA. In the absence of, or consistent with, adopting these international guidelines it is recommended that the FDA seek input from its internal pharmacologists/toxicologists as to what they consider be a "safe" dose (i.e., based on submitted acute and limited, repeat-dose animal toxicity studies) at which to accept IND applications directed at first in human Phase I clinical trials of investigational drugs.

At the Public Hearing there was discussion as to whether first in human studies of radioactive drugs using a "microdose" concept should be addressed via a change to the current 21 CFR 361.1 regulations or the development of respective, "exploratory" Investigational New Drug (IND) application guidelines. Regarding this issue, the FDA indicated that it is a difficult process to effect revised regulations. I find this statement somewhat curious in recognition that 1) the Federal government does have in place an Administrative Procedures Act, which outlines the processes and procedures for modifying existing Federal regulations; and 2) other Federal agencies, such as the Nuclear Regulatory Commission, routinely adopt new or revised regulations. Should the FDA feel that it would be easier to implement the "microdosing" concept via guidance surrounding an "exploratory" IND mechanism, I have concerns that other requirements (e.g., cGMP compliance) routinely associated with the FDA's acceptance of INDs will be applied coincidently to radioactive drugs used under this process. Thus I cannot be fully supportive of this approach until such time that I have had the opportunity to review all of the requirements surrounding the submission of such an "exploratory" IND application. In addition, I foresee where the FDA may encounter internal pressures regarding the issuance of such guidance since it will likely result in IND standards for applicable radioactive drugs that are significantly different than the standards for non-radioactive drugs. Moreover, for

[2] See Bergstrom M, Grahnen A, Langstrom B; Positron emission tomography microdosing: a new concept with application in tracer and early clinical drug development. Eur J Clin Pharmacol 59: 357-366, 2003.

many applicable radioactive drugs there will be no desire to pursue subsequent marketing; thus resulting in perpetual INDs. Albeit, I do recognize that once an initial clinical assessment of the (lack of) pharmacologic effect of the radioactive drug has been completed, the "exploratory" IND could be terminated and the radioactive drug further studied under the current 21 CFR 361.1 regulations. However, this approach would seem to involve a somewhat convoluted process and it might be easier to simply amend the "exploratory" IND to include additional human research studies involving use of the respective radioactive drug. Conversely, I recognize that the FDA may be unwilling to permit first in human studies with radioactive drugs based solely on the review of animal toxicity data by a local RDRC. However, an approach that could be taken to address this issue (i.e., assuming that the FDA is willing to pursue a revision of the 21 CFR 361.1 regulations) would be to require that, for any first in human radioactive drug study approved by the RDRC based on limited animal toxicity data, the RDRC must immediately submit the respective toxicity and dosage information for review by the FDA. This approach would be consistent with current 21 CFR 361.1 requirements for the RDRC to immediately submit a "Special Summary Report" if a RDRC-approved study involves greater than 30 subjects or pediatric subjects. In addition, I feel that addressing the first in human "microdose" concept as part of the 21 CFR 361.1 regulations would serve to limit this concept to radioactive drugs and avoid external pressures to extend it to other drug classes.

Regardless of whether the "microdose" concept is addressed via revisions to 21 CFR 361.1 or the "exploratory" IND mechanism, the initial introduction of a radioactive drug into humans based on valid, limited animal toxicity data should involve certain basic physiological assessments to ensure safety of the "microdose" of the radioactive drug. It is recommended that such a requirement for physiological assessments be limited with regard to both scope and application. For example, the physiological assessments should involve basic pre- and post-administration measures of blood pressure, respirations, heart rate, temperature, and, perhaps, a pre-and post-administration CBC; with emphasis placed on identifying statistically significant alterations in these parameters. Performance of these physiological assessments should be limited to the first three (3) adult subjects, with a requirement for repeat physiological assessments on an additional three (3) subjects if one of the initial group of subjects demonstrates a significant alteration in any physiological parameter evaluated. If two (2) or more of the initial group of three (3) subjects or of the added group of three (3) subjects demonstrates a significant alteration in a physiological parameter; the administered "microdose" of the radioactive drug must be reduced and re-evaluated in a similar manner (i.e., consistent with the design of a classic Phase I single dose, dose-ranging study). These physiological assessments should be repeated at the time that the radioactive drug is introduced into pediatric patients; with perhaps consideration given to performing repeat assessments on each of certain pediatric age-range groups (e.g., neonate–4 years old, 5-10 years old, 11-18 years old). Since, as proposed previously, the FDA would be made aware of the RDRC's approval of a first in human study involving a radioactive drug, the FDA can, at its discretion, follow up with a request for the outcome of these physiological assessments or require that they be submitted as part of the RDRC's Annual Report.

Note that I do not feel that biological products should be automatically excluded, as a class, from approval under the current or revised 21 CFR 361.1 regulations or the "exploratory" IND mechanism. Certain biological products, such as peptides, are not typically associated with an antigenic response. Also, current technology is focused on the development of "humanized" proteins as drug substances so as to minimize the potential for antigenic responses. Thus, I feel that microdoses of radioactive analogs of such biological products may, in fact, be administered safely to human subjects under either of these regulatory frameworks. Hence, I recommend that this restriction, if imposed, be limited to radioactive heterogeneous proteins.

Should the 21 CFR 361.1 regulations remain as currently worded, guidance is needed in two areas: 1) how should an investigator or RDRC confirm that a radioactive drug causes no clinically detectable pharmacological effect in humans; and 2) is it acceptable to use, under these regulations, a radioactive drug wherein the chemical structure of the drug previously evaluated in humans has been altered for the purpose of radiolabeling the drug?

Regarding the first of these issues, it is my assumption that any drug evaluated previously in humans in the U.S. would have been the subject of an IND application and corresponding safety assessments. Thus information confirming the lack of a clinically detectable pharmacological effect in humans should be available from the sponsor's Phase I single dose, dose-ranging studies. Herein lies an area wherein increased cooperation between the FDA and RDRCs would be beneficial. I.e., while such Phase I safety data may not be directly available to the investigator (i.e., of the radioactive drug) or RDRC through publication of this information or otherwise from the sponsor, the investigator or RDRC could request a letter from the sponsor allowing the FDA to access the IND for this drug in support of the investigator's RDRC application. The FDA would subsequently inform the responsible RDRC of the acceptability of the proposed dosage of the radioactive drug. Based on my experience as a RDRC Chair, a more difficult situation occurs when an investigator requests RDRC approval of the use of a radioactive drug based on prior human studies with the radioactive drug conducted at another U.S. or foreign site. Typically such a request includes references to published articles or abstracts and may include a letter from a representative of the external site specifying that "no pharmacological effects or adverse events were observed". However, none of these supporting documents outlines the specific safety assessments that were performed to come to this conclusion. Assuming that the U.S. external site is in compliance with FDA regulations, the first in human evaluation of the radioactive drug should have been conducted under a FDA-accepted IND application. Thus, physiological assessments documenting the safety of this radioactive drug should be available from or through its sponsor, as described above. However, as previously discussed, the requirements of certain foreign countries governing the human use of radiotracers are far less extensive than those of the FDA. If the referenced first in human study of the radioactive drug was conducted in one of these foreign

countries, then there may not be required safety assessments available for FDA and RDRC consideration. (This situation, in fact, supports the need for international harmonization of the regulations governing the human use of radioactive drugs.) In summary, for those situations wherein published literature or other human data are available to suggest that the proposed dose of the radioactive drug will not produce a clinically detectable pharmacological effect, but information regarding the specific safety assessments conducted to support this conclusion is not available, I recommend that FDA guidance should specify that the RDRC should require, as a condition of approving locally the human use of the radioactive drug, that certain initial, basic physiological assessments (i.e., as described above) must be performed.

I must admit that I was greatly disturbed to learn at the Public Meeting that the FDA is aware of RDRCs that approved the use of radioactive drugs wherein the chemical structure of the drug previously evaluated in humans had been altered for the purpose of radiolabeling the drug (e.g., the introduction of a foreign [F-18] fluorine atom into the chemical structure of the drug). The addition of a foreign atom or molecule to the chemical structure of a drug for this purpose results in a different drug (i.e., a different chemical entity), and unless this different drug has also been previously evaluated in humans the involved RDRCs are in violation of the 21 CFR 361.1 regulations. Note that, as I expressed at the Public Meeting, such noncompliance on the part of certain RDRCs has the potential to result in local investigator criticisms of those RDRCs that are attempting to be in full compliance with the regulations and to create an uneven playing field with regard to investigator competition for limited research funding. Thus, I feel that the FDA must provide explicit guidance regarding the acceptability/non-acceptability of this practice.

2. *Radiation Dose Limits for Adult Subjects*: It is noted that the radiation dose limits for adult subjects specified in Section 361.1(b)(3)(i) were based on occupational radiation protection criteria established by the Nuclear Regulatory Commission (NRC) under 10 CFR 20.101. It was the FDA's thinking at the time of initial development of the 21 CFR 361.1 regulations that these criteria would enable a potential research subject to make an informed decision regarding participation in a research study because the subject would, in effect, be deciding whether he or she is willing to assume the same degree of risk as a radiation worker for the duration of the study.

   I feel that the radiation dose limits for adult subjects specified in 21 CFR 361.1 should continue to be based on occupational dose limits for the reasons previously considered by the FDA. However, the metrics for addressing radiation risk that appear currently in these regulations are outdated. Based on the discussions at the Public Meeting, I feel that the 21 CFR 361.1 regulations should adopt, as a radiation dose limit for adult subjects, the International Commission on Radiation Protection (ICRP) annual (cumulative) "effective dose" limit for adult radiation workers. The "effective dose" metric appears to be currently the most accepted method for

describing radiation risk, and takes into account individual organ sensitivities (i.e., thus eliminating the need to address radiation dose limits for individual organs). In addition, it will facilitate addressing the overall radiation risk resulting from the systemic administration of a radioactive drug and the application, for the purpose of the research study, of additional, limited-area radiation exposure procedures (e.g., chest X-ray, CT, transmission scan). Moreover, adoption of the ICRP radiation dose limit would be consistent with current efforts to harmonize internationally the regulations that govern the drug development and approval process. Rather than addressing the current, specific ICRP occupational dose limit, consideration should be given to incorporating the following statement into the 21 CFR 361.1 regulations: "The radiation dose limit for adult subjects must be less than or equal to the annual (cumulative) radiation dose limit for adult radiation workers specified in current ICRP regulations." This approach would obviate the need to revise the 21 CFR 361.1 regulations as any changes are made to the respective ICRP standards.

Consistent with the consideration for adopting occupational radiation dose limits as the appropriate standard for 21 CFR 361.1, there should only be different dose limits for different adult age groups if the respective regulatory (NRC) or expert commission (ICRP) standards are also revised to address this concept.

The current 21 CFR 361.1 regulations (Section 361.1 (b)(3)(i)) specify that "under no circumstances may the radiation dose to an adult research subject from a single study *(emphasis added)* or cumulatively from a number of studies conducted within 1 year be generally recognized as safe if such dose exceeds the following" --- (table of "single dose" and "annual and total dose commitment" limits). As stated above, I feel that these regulations should be revised to address only an annual (cumulative) "effective dose" limit based on the current ICRP adult occupational worker standard. Note that none of the current regulatory (e.g., NRC) or expert commission (e.g., ICRP, National Commission on Radiation Protection) adult occupational dose limit standards address a "single study" or "single dose" limit, and it is unclear why this criterion was included in the current 21 CFR 361.1 regulations or the basis for the respective radiation dose limit values. Should the 21 CFR 361.1 radiation dose limit criteria remain as written, guidance is needed on what is meant by a "single study" and/or the relationship of a "single study" radiation dose to the "single dose" limits specified in the table. For example, does a "single study" mean the one time administration of a single radioactive drug; or multiple administrations of a single drug as part of a single study; or the administration of multiple radioactive drugs as part of a single study; or the administration of multiple radioactive drugs during a single PET scanning session?

Clarification is also needed as to how the previously quoted Section 361.1 (b)(3)(i) statement relates to a research subject who may agree to participate, during a one year period, in a research study involving a radioactive drug (i.e., subject to the 21 CFR 361.1 regulations) and one or more additional research studies which do not involve a radioactive drug subject to these regulations, but which involve exposure to other sources of ionizing radiation. Of further note regarding this issue, Section 361.1

(b)(3)(iii) states that "Radiation doses from x-ray procedures that are part of the research study (i.e., would not have occurred but for the study) shall also be included" in determining the total radiation doses and dose commitments. Hence, must the radiation doses that the subject receives from participation in the research studies that are not subject to RDRC approval be added to the radiation dose that this subject receives from participation in the RDRC regulated study in order to ensure that the 21 CFR 361.1 adult annual (cumulative) radiation dose limits are not exceeded? If so, how is the RDRC suppose to be aware of all of the research studies involving exposure to ionizing radiation in which a given subject may participate? Attempting to keep track of such total radiation exposures on a subject-by-subject basis would be an extremely difficult and tedious process.

3. *Assurance of Safety for Pediatric Subjects*: The FDA regulations at 21 CFR 361.1 currently allow (i.e., without the requirement to obtain an IND) for the study of radioactive drugs in subjects less than 18 years of age if 1) the study presents a unique opportunity to gain information not currently available, requires the use of research subjects less than 18 years of age, is without significant risk to subjects, and is supported with review by qualified pediatric consultants to the RDRC; and 2) the radiation dose does not exceed 10 percent of the adult radiation dose limit specified in Section 361.1 (b)(3)(i). It is further noted that Section 361.1 (d)(9) requires the investigator to also "obtain the review and approval of an institutional review board that conforms to the requirements of part 56 of this chapter."

   I feel that the respective provisions of 21 CFR 361.1 combined with the 21 CFR 50 Subpart D regulations (i.e., *Additional Safeguards for Children in Clinical Investigations*), which govern institutional review board (IRB) approval of research studies involving children, provide adequate safeguards for pediatric subjects during the course of a research project intended to obtain basic information about a radioactive drug. Radioactive drug studies that meet the requirements of both of these sets of regulations should not be subject to a requirement for prior submission of an IND. In this regard, I feel that radioactive drug research studies approvable under 21 CFR 361.1 have the potential to contribute greatly to our understanding of the pathophysiology of diseases or conditions common or exclusive to children. Moreover, radioactive drug research studies conducted under 21 CFR 361.1 may contribute important pharmacokinetic information applicable to the design of Phase IV clinical trials directed at evaluating the safety and effectiveness of reduced dosages of (non-radioactive) approved drugs in pediatric patients. Subjecting such basic research studies to the increased requirements associated with the submission of an IND would likely have the effect of diminishing their conduct.

   It should be noted that radioactive drug research studies that meet the requirements of the current 21 CFR 361.1 regulations can only be approved by an IRB under 21 CFR 50.53 (i.e., "Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subject, but likely to yield generalizable knowledge about the subjects' disorder or condition") or 21 CFR 50.54 (i.e., "Clinical investigations not otherwise approvable that present an opportunity to understand,

prevent, or alleviate a serious problem affecting the health or welfare of children"). In order to avoid the additional DHHS notification and review requirements associated with approval of such research studies under 21 CFR 50.54, it will be imperative that the involved research community develop a strong justification for why the administration of applicable radioactive drugs to children is felt to represent only a "minor increase over minimal risk" (i.e., consistent with the provisions of 21 CFR 50.53). It should be noted that such a justification will be required whether or not the pediatric use of the radioactive drug is subject to the provisions of 21 CFR 361.1 or an IND application. However, it is felt that approval of the pediatric research use of a radioactive drug under the regulatory framework of 21 CFR 361.1 will lend support to this justification since as per Section 361.1 (a) "Radioactive drugs are generally recognized as safe and effective *(emphasis added)* when administered, under the conditions set forth in paragraph (b) of this section, to human research subjects ---."

In the event that the 21 CFR 361.1 regulations are revised to permit first in human studies based on a microdosing concept; should these revised regulations also be applicable to children? It is my opinion that the research use of any unapproved radioactive drug in children must be preceded by its use in adults. Albeit likely a decision that will be made by any RDRC and/or IRB functioning in a responsible manner, I feel that the 21 CFR 361.1 regulations, if revised to address the microdosing concept, should also include a requirement that the radioactive drug must be used in adults before can be used for research studies in children. Any proposed first in human research use of a radioactive drug in children should be subject to prior submission and FDA acceptance of a respective IND application.

I do not feel that the current 21 CFR 361.1 radiation dose limits for pediatric subjects are appropriate. The requirement that radiation dose limits for children shall not exceed 10 percent of the adult limits is arbitrary and does not take into account the fact that many adolescents have a greater body surface area than the average adult. Moreover, this leads frequently to research submissions wherein the amount of the proposed radioactivity (i.e., mCi) dosage to be given to child-subjects is restricted so as to meet the 10% radiation dose limit requirements. This situation results often in child-subject inconvenience (e.g., long imaging times) and/or imaging outcomes of less than optimal quality. Rather, I feel that the 21 CFR 361.1 regulations should reference an appropriate nomogram for the determination of proper pediatric dosages; i.e., based on individual child surface area and standard adult dosage considerations. The resulting estimated radiation dose to the child-subject, as determined using pediatric radiation dose estimates for the radioactive drug that conform to the child-subject's age grouping, should not exceed the maximum adult effective dose limit established under the 21 CFR 361.1 regulations (*vide supra*).

4. *Quality and Purity of the Radioactive Drug:* In accordance with Section 361.1 (d)(6), the RDRC is required to assure that the radioactive drug used in the research study meets appropriate standards of strength, quality and purity as needed for safety and be of such uniform and reproducible quality as to give significance to the study. There

is, however, no further discussion as to what constitutes "appropriate standards" for the radioactive drug.

The preparation of PET radioactive drugs for clinical and research use is currently subject to the provisions of Section 121 (*Positron Emission Tomography*) of Food and Drug Administration Modernization Act of 1997 (FDAMA). This congressional act defines the term "compounded positron emission tomography drug" as "a drug that (a) exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for the purpose of providing dual photon positron emission tomographic diagnostic images; and (b) has been compounded by or on the order of a practitioner who is licensed by a State to compound or order compounding for a drug described in subparagraph (a) and is compounded in accordance with that State's law for a patient or for research (*emphasis added*), teaching or quality control." Section 121 of FDAMA further specifies that a compounded PET radioactive drug shall be considered to be adulterated "if the methods used in, or the facilities and controls used for, its compounding, processing, packing, or holding do not conform to or are not operated or administered in conformity with the positron emission tomography compounding standards and the official monographs of the United States Pharmacopeia to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, that it purports or is represented to possess." While it may be argued that the preparation of PET radioactive drugs administered under 21 CFR 361.1 is not subject to Section 121 of FDAMA (i.e., the PET radioactive drug is not being "provided for diagnostic images"); I feel that it is difficult to justify, in the absence of other appropriate standards, not also applying the United States Pharmacopeia (USP) compounding standards (i.e., USP Chapter <823>, *Radiopharmaceuticals for Positron Emission Tomography-Compounding*) and, where applicable, USP monographs to these PET radioactive drugs. Similarly, I feel that all non-PET radioactive drugs administered under 21 CFR 361.1 should be prepared in compliance with USP Chapter <797>, *Pharmaceutical Compounding – Sterile Products*. Consistent with Section 121 of FDAMA, for a PET or non-PET radioactive drug wherein a USP monograph exists, the final standards (i.e., limits) for strength, quality and purity should be in agreement with this monograph. For a PET or non-PET radioactive drug wherein a USP monograph does not exist, final acceptable standards (i.e., limits) for strength, quality and purity should be determined by the RDRC; taking into account respective standards appearing in the USP monographs for other radioactive drugs.

It should be emphasized that although the requirements outlined in USP Chapters <823> and <797> may be considered less stringent than the FDA's current Good Manufacturing Practice (cGMP) standards, they do provide for adequate safety of research subjects and for uniform and reproducible quality of the radioactive drug. Moreover, it is felt that these USP Chapters provide for an appropriate level of stringency taking into account the basic research nature of studies approvable under 21 CFR 361.1. Both of these USP chapters are "official" USP chapters and are therefore subject to enforcement by the FDA. In addition, the USP mechanisms for chapter and monograph development and revision are considerably more flexible than

the processes for the development and revision of FDA regulations; while also providing for respective input from the FDA.

5. *Exclusion of Pregnant Women*: Section 361.1(d)(5) requires that each female research subject of childbearing potential state in writing that she is not pregnant or, on the basis of a pregnancy test, be confirmed as not pregnant before she may participate in any research study involving a radioactive drug administered under 21 CFR 361.1.

   I feel that all women of childbearing potential (i.e., women who are not at least one year post-menopause or who have not undergone a surgical sterilization procedure) should be required to undergo a urine pregnancy test within a short time period (i.e., within 24 or 48 hours) prior to the receipt of a radioactive drug administered under 21 CFR 361.1. The interval between pregnancy testing and the receipt of the radioactive drug may be longer; provided, however, that the corresponding research protocol also addresses a requirement for an acceptable method of contraception commencing prior to or at the time of this pregnancy testing.

   Commercially available urine pregnancy tests are readily available, inexpensive, easy to perform and interpret, and reasonably accurate. In addition, it must be recognized that subjects receive no direct benefit from participation in research studies approvable under 21 CFR 361.1. These considerations, combined with the safety and liability concerns associated with fetal exposure to ionizing radiation, provide ample justification for the routine employment of pregnancy testing prior to administration of radioactive drugs under 21 CFR 361.1.

6. *RDRC Membership*:

   a. Under Section 361.1(c)(1), a RDRC must include the following expertise: (1) a physician recognized as a specialist in nuclear medicine; (2) a person qualified to formulate radioactive drugs, and (3) a person with special competence in radiation safety and radiation dosimetry. Currently there is no membership requirement for an individual with expertise in pharmacology and/or toxicology.

      If the 21 CFR 361.1 regulations remain as currently written, I do not feel that there should be a requirement to also include a pharmacologist or toxicologist as part of the RDRC membership. It should be emphasized that Section 361.1(c)(1) also specifies:

      > "Membership shall be sufficiently diverse to permit expert review of the technical and scientific aspects of proposals submitted to the committee. The addition of consultants in other pertinent medical disciplines is encouraged."

      In my opinion, the current required members of the RDRC have a sufficient level of expertise to determine whether or not the proposed dosage of a radioactive drug will cause any clinically detectable pharmacological effect; i.e., based on

submitted data available from the published literature or from other valid human studies. This is especially true in consideration of the fact that radioactive drugs approved under 21 CFR 361.1 are typically administered in tracer quantities (i.e., to avoid perturbing the physiological system being studied) and, thus, represent a very small fraction of the dosage described in the published human literature. If there are respective questions or concerns, the RDRC already has the ability to include, as members or consultants, individuals with appropriate pharmacology or toxicology expertise.

If, however, the 21 CFR 361.1 regulations are revised to permit first in human studies of "microdoses" of radioactive drugs based on valid, limited animal toxicity data, then I feel that there should be a requirement for an individual with toxicology expertise as a member of the RDRC.

b. Under Section 361.1(c)(4), changes in the membership of a RDRC must be submitted to the FDA as soon as, or before, vacancies occur on the committee. The current regulations do not, however, specifically require that FDA approve RDRC membership changes before new members assume committee responsibilities.

I do not feel that it is necessary to revise the current 21 CCR 361.1 regulations to allow the FDA to review and approve the qualifications of a proposed new member before that member can assume committee responsibilities. As stated above, Section 361.1(c)(4) specifies that "Changes in membership and applications for new members shall be submitted to the Food and Drug Administration as soon as, or before, vacancies occur on the committee". Hence, if a RDRC is operating in compliance with these regulations, it will be highly unlikely that more than one committee meeting will occur before the FDA has received notice of a membership change and has had the opportunity to review and respond to this notice. This section of the 21 CFR 361.1 regulations also specifies:

> "Each Radioactive Drug Research Committee shall be specifically approved by the Center for Drug Evaluation and Research. --- Approval shall be based upon an assessment of the qualifications of the members of the committee, and the assurance that all necessary fields of expertise are covered. Approval of a committee may be withdrawn at any time for failure of the committee to comply with any of the requirements of this section."

Thus, while not explicitly stated, I do believe that the FDA already has the authority to approve or disapprove changes to the RDRC membership. Furthermore, it must be recognized that a requirement for the FDA to approve prospectively changes in the RDRC membership can result in a situation wherein the RDRC cannot meet quorum requirements and therefore cannot review, in a timely manner, applicable research proposals. This can lead to losses of research opportunities and/or respective funding.

7. *Additional Considerations*: Section 361.1 (a) specifies the following:

> "Radioactive drugs are generally recognized as safe and effective when administered, under conditions set forth in paragraph (b) of this section, to human research subjects during the course of a research project intended obtain basic information regarding the metabolism (including kinetics, distribution and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial). Certain basic research studies, e.g., studies to determine whether a drug localizes in a particular organ or fluid space and to describe the kinetics of that localization, may have eventual therapeutic or diagnostic implications, but the initial studies are considered to be basic research within the meaning of this section."

I feel that these statements, as currently worded, are contradictory and frequently result in undue concerns, confusion and limitations as to what types of research studies can and cannot be approved by a RDRC. For example, is a research study directed at modeling the kinetics of a radioactive drug so as to optimize its subsequent use for evaluating a pathophysiological process approvable under these regulations? Is a research study directed at evaluating the appropriate (mCi) dosage of [O-15] water for assessing blood flow to the peripheral musculature of diabetics approvable under these regulations? It is unclear to me why it is, in fact, necessary for these regulations to make a distinction between "basic research studies" and research studies directed at performing initial assessments of the effectiveness of a radioactive drug for a potential diagnostic or therapeutic use. In this regard, it should be emphasized that the additional provisions of 21 CFR 361.1 ensure that the radioactive drug is generally safe. Thus, whether the focus of the proposed study is to obtain "basic research" information or to conduct an initial assessment of the effectiveness of a radioactive drug for a diagnostic or therapeutic indication has no bearing on the safety of the involved research subjects. Therefore I feel that Phase I and II clinical trials should be permitted to be conducted under the 21 CFR 361.1 regulations. Should any investigator/sponsor decide to pursue subsequent marketing of the radioactive drug, then the conduct of multi-center Phase III clinical trials should be subject to the submission of an IND application; the latter being supported by the data obtained from the research studies previously conducted under 21 CFR 361.1.

I do, however, recognize that the safety of the involved research subjects could be impacted if the results of unsubstantiated radioactive drug studies were to be used directly to guide subsequent therapeutic decisions. Thus, I feel that the 21 CFR 361.1 regulations should continue to specify that the results of radioactive drug research studies approvable under these regulations cannot be used for immediate diagnostic purposes and/or to guide subsequent treatment decisions. (Note that the 21 CFR 361.1 limitations on radiation dose would preclude the conduct of any research study focused at using a radioactive drug for the direct treatment of a disease or condition.) In summary, it is recommended that section 361.1 (a) be revised as follows:

"Radioactive drugs are generally recognized as safe and effective when administered, under conditions set forth in paragraph (b) of this section, to human research subjects during the course of a research project intended obtain basic information regarding the metabolism (including kinetics, distribution and localization) of the respective drug, or regarding human physiology, pathophysiology, or biochemistry, and/or regarding the potential diagnostic or therapeutic effectiveness of the respective drug; but not intended for immediate diagnostic use or to guide subsequent therapeutic decisions. Multi-center research studies conducted in support of potential marketing of the radioactive drug shall be subject to the submission and FDA acceptance of an Investigational New Drug application."

In conclusion, please accept my appreciation for being provided the opportunity to provide input regarding the FDA's consideration of possible revisions to the 21 CFR 361.1 regulations. Please do not hesitate to contact me if I can be of any further assistance in these efforts.

Respectfully submitted,

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